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(71) Applicant: TRANSON, LLC [-/US]; 650 California Street, 25th Floor, San Francisco, CA 94108 (US).

(72) Inventors: BOND, Geoffrey; 20 E. Lake Street, Lakewood, NY 14750 (US). PETERSON, Thomas, M.; 4249 Neptune Street, Erie, PA 16506 (US).

(74) Agent: HACKLER, Walter, A.; 2372 S.E. Bristol, Suite B, Newport Beach, CA 92660 (US).

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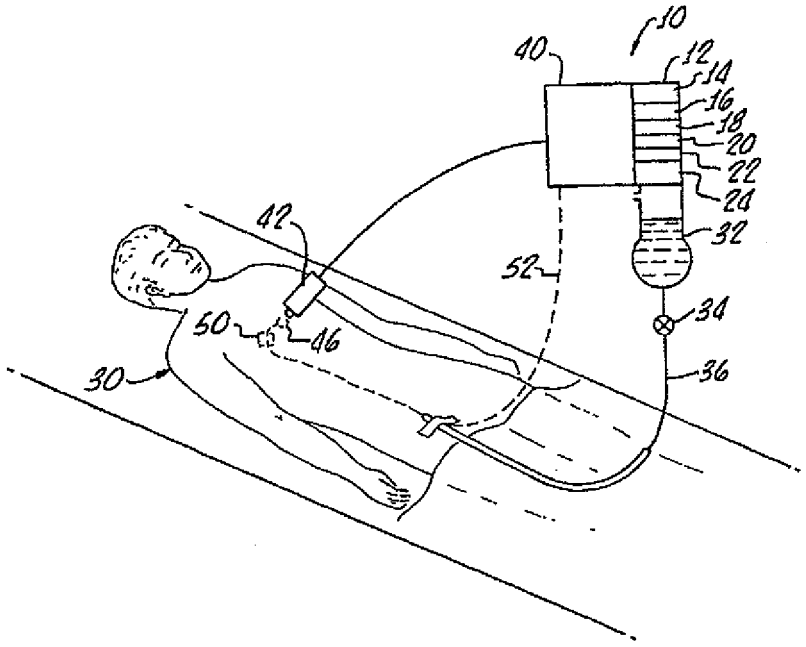
(54) Title: METHOD AND APPARATUS FOR EMERGENCY TREATMENT OF A PATIENT EXPERIENCING A THROMBOTIC VASCULAR OCCLUSION



(57) Abstract

This invention is an acute care method, and apparatus (10) for treating a patient experiencing a thrombotic vascular occlusion that includes introducing a selected dose of an active agent proximate a vascular occlusion in the patient in order to lyse the vascular occlusion, radiating the vascular occlusion, and active agent.

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METHOD AND APPARATUS FOR EMERGENCY TREATMENT OF PATIENTS EXPERIENCING A THROMBOTIC VASCULAR OCCLUSION

The present invention is generally related to a method and apparatus for pre-hospital or initial treatment of patients experiencing a thrombotic vascular occlusion, and is more particularly directed to an emergency application of ultrasound and an agent for lysing vascular occlusions or thrombi. Importantly, the agent may not have activity for lysing vascular occlusions without application of ultrasound.

Thrombosis can cause partial or total occlusion of blood vessels which leads to a number of important cardiovascular complications, including unstable angina, acute myocardial infarction (heart attack), cerebral vascular accidents (stroke) pulmonary embolism, deep vein thrombosis and arterial thrombosis.

It is well known that acute myocardial infarction is one of the greatest causes of death in the United States, and it has been recognized that time is of the essence in successfully treating individuals undergoing acute myocardial infarction. Many hospitals and caregiving institutions have established coronary care units with trained personnel and equipment for treating a patient in the shortest time possible upon arrival. However, important time is lost during the delivery of patients to hospitals.

Removal or lysing of vascular occlusions, or clots, may be accomplished through a variety of

agents such as, for example, urokinase, streptokinase, aspirin and tissue plasminogen activators, tPA. These clot dissolving agents are generally used in order to lyse clots which have formed in the coronary arteries.

These agents are typically injected into the bloodstream or organ close to the position of the clot. Unfortunately, such agents have a side effect of causing undesirable bleeding in the patient. Thus, patients who may have an ulcer or other bleeding disorder are especially difficult to treat with systemic anticoagulants. Aspirin has found wide use as a clot inhibitor, particularly with respect to clots on the arterial side of circulation. However, aspirin is used as an adjuvant agent to prevent thrombosis and has little if any effect on an established blood clot.

Ultrasound has found use in the dissolution of vascular occlusions. For example, U.S. Patent Nos. 5,269,291, 5,318,014, 5,362,309, 5,431,662 and 5,474,531, describe intravascular ultrasonic tools for the dissolution of intravascular blockages.

More recently, transcutaneous ultrasound has been found to enhance the activity of thrombolytic agent, for example, see U.S. Patent Nos. 5,509,896 and 5,695,460. All of the hereinabove referenced patents have been assigned to the assignee of the present application.

Thus, while it has been recognized that the use of ultrasound with an active agent enhances the activity of the agent in lysing of a vascular occlusion, other synergistic properties have not been heretofore discovered. For instance, it has

been found in accordance with the present invention that ultrasound shortens the onset of thrombolysis activity of an agent such as, for example, microbubbles or tPA. Accordingly, more rapid onset of dissolution of clots results in less damage from the vascular occlusion because of more rapid opening of the blood vessel and in the restoration of tissue perfusion. In addition, the combination of certain agents and ultrasound could reduce the likelihood of excess bleeding which may significantly increase the likelihood of survival by a patient.

SUMMARY OF THE INVENTION

A method in accordance with the present invention for providing acute care treatment of a patient experiencing thrombotic vascular occlusion generally includes the steps of introducing a selected dose of an agent for acting on a vascular occlusion in the patient in order to lyse the vascular occlusion and irradiating the vascular occlusion and active agent in order to shorten onset and accelerate the effectiveness of lysing action of the agent. In view of the well known urgency of heart attack and stroke matters, i.e., cell death is directly proportional to time, it is of utmost importance to enhance the onset and accelerate the effectiveness of the active agent in lysing the vascular occlusion.

An "active agent" as used herein is meant to include an agent having little or no lysing activity without ultrasound, but exhibiting lysing activity with ultrasound.

The method in accordance with the present invention applies to coronary, cerebral and

peripheral vascular (venous or arterial) occlusions and it is found that the active agent may be a thrombolytic agent, anticoagulants, agents which alter blood viscosity and supply nuclei to facilitate microstreaming, cavitation agents that enhance clot disruption (e.g., Hespan, Pentaspan, an intravenous fat emulsion such as intralipid, liposyn, a microbubble medium, and an antiplatelet agent or other suitable lysing agents).

Accordingly, apparatus in accordance with the present invention, includes a self-contained mobile unit for paramedic or emergency treatment of a patient experiencing thrombotic vascular occlusion. In view of the utmost importance of availability, the apparatus includes a plurality of active agents for dissolution of vascular occlusions. A tutored paramedic or physician selects an agent based upon the indication of patient bleeding and intravenously supplies the agent to the vascular occlusion along with transcutaneously radiating the vascular occlusion.

Accordingly, one method in accordance with the present invention includes application of ultrasound transcutaneously. Under certain situations, the ultrasound may be applied intravascularly and the active agent may be introduced proximate the vascular occlusion by direct injection.

BRIEF DESCRIPTION OF THE DRAWINGS

The advantages and features of the present invention will be better understood by the following description when considered in conjunction with the accompanying drawings, in which:

Figure 1 is a diagram of apparatus in accordance with the present invention which also illustrates the method in accordance with the present invention; and

Figure 2 is a graph of lysing effectiveness with and without ultrasound as a function of time.

DETAILED DESCRIPTION

With reference now to Figure 1, there is shown apparatus 10 for effecting pre-hospital or emergency treatment of a patient experiencing thrombolytic vascular occlusion which includes a self-contained mobile unit 12. As represented by boxes 14, 16, 18, 20, 22, 24, a plurality of active agents for dissolution of vascular occlusion are provided with at least one of the active agents being selected by a paramedic or physician for intravenous introduction into a patient 30 by a vial 32, valve 34 and line 36 which, in combination, provide intravenous means for introducing the selected agent into the patient 30. A vascular occlusion in the present application includes coronary occlusions, cerebral occlusions and peripheral occlusions both venous and arterial. A portable ultrasonic oscillator 40 and transducer 42, in combination, provide a means for transcutaneously radiating a vascular occlusion as indicated by the dotted line at 46. The oscillator 40 may be battery powered, connected to a vehicle electrical system, or connected to a conventional electrical source (not shown) by any conventional means. It should be appreciated that multiple oscillators and transducers (not shown) may be utilized, each having a desirable operating range and properties.

It should be appreciated that ultrasound may be applied intravascularly under proper circumstances, and, in this instance, a miniature transducer, and connected to the oscillator 40 as indicated by the dotted line 50 may be utilized. In this regard, reference is made to U.S. Patent No. 5,269,291, 5,318,014, 2,062,309, 3,431,662, and 4,474,531 which are hereby incorporated in toto by this specific reference thereto as indicating intravascular transducers which may be utilized in accordance with the present invention, all of these patents being assigned to assignee of the present invention.

The transducer 42 may be of any suitable design, for example, as set forth in U.S. Patent No. 5,879,314 which is incorporated herewith in toto by this reference thereto for the purpose of illustrating the types of transcutaneous transducers which may be suitable for use in accordance with the present invention. The effective frequency range may be from between about 10 kHz to about 2 mHz, with a desirable frequency range being between about 20 kHz and about 500 kHz and another desirable frequency range being between 20 kHz and 50 kHz. The oscillator 40 may be of any suitable type as set forth in any number of the hereinabove referenced U.S. patents.

As hereinabove noted, timing and selection of appropriate lysing agents is of utmost importance.

For example, a criteria for selection between an echo contrast agent such as sonicated albumin, perfluorocarbon, a lysing or thrombolytic agent such as streptokinase or tPA, an anticoagulant such as heparin, antiplatelet agents, such as platelet

receptor, like a GP IIb-IIIa inhibitor, such as blockers, Aggrastat, Integrillin, a GP IIb-IIIa platelet inhibitor, Reopro, a hyperalimentation agent such as intravenous fat emulsions, intralipid and liposyn, or another alternative agent such as Hetastarch or other artificial colloidal solutions, such as Pentaspan®, may be as follows.

If there is no indicated bleeding, or significant risk of bleeding, a thrombolitic agent may be selected. If there is possible indicated or risk of bleeding, a GP IIb-IIIa inhibitor may be selected. If there is an absolute contraindication due to risk of bleeding, a microbubble, Hetastarch or Pentaspan is preferably selected.

Other indications may be utilized for agent selection.

It should also be appreciated that a combination of agents may be utilized, for example, an echocontrast agent may be used in combination with a thrombolytic agent. For example, an echocontrast agent may be a perfluorocarbon, such as, for example, the dodecafluropentane colloid dispersion. The echocontrast agent may be a microbubble medium such as free gas bubbles, stabilized gas bubbles, colloidal suspensions, emulsions and aqueous solutions other than dodecafluropentane. A thrombolytic agent may be any agent having suitable activity such as, for example, streptokinase, staphlokinase, urokinase or a tissue plasminogen activator (tPA). These agents are set forth herein only by way of example and it should be appreciated that, as hereinabove recited, any thrombolytic agent has possible use in accordance with the present invention.

As hereinabove noted, a Hetastarch such as HESPAN®, which is a plasma volume expander, has been found to be effective when used in combination with ultrasound for the lysing of vascular occlusions.

Hetastarch is an artificial colloid derived from a waxy starch composed almost entirely of amylopectin. Hydroxyethyl ether groups are introduced into the glucose units of the starch and the resultant material is hydrolyzed to yield a product with a molecular weight suitable for use as a plasma volume expander and erythrocyte sedimenting agent.

As also hereinabove noted, a colloid suspension or pentastarch, such as Pentaspan®. Pentaspan® or Pentastarch is an artificial colloid derived from a waxy starch composed almost entirely of amylopectin. Hydroxyethyl ether groups are introduced into the glucose units of the starch and the resultant material is hydrolyzed to yield a product with a molecular weight suitable for use in an erythrocyte sedimenting agent.

Additionally, the radiation by ultrasound may include continuous or pulse radiation, still more particularly by way of example only, the amount of active agent introduced may be in concentration less than about 2000 microliters.

The combination of ultrasound has the unique effect of accelerating the onset of lysing activity of a GP IIb-IIIa antiplatelet inhibitor such as Reopro or a GP IIb-IIIa blocker such as, for example, Aggrastat and Integrillin.

Figure 2 shows a percent of lysing of human blood clots in vitro when blood clots were incubated with Aggrastat alone at the blood concentration achieved in patients being treated with this agent alone at a concentration which is similar to that given therapeutically to patients and in combination with ultrasound at a frequency of 20 kHz applied transcutaneously. It is evident that in five minutes the use of ultrasound more than doubles the lysing activity of the Aggrastat with the overall lysing activity of being less enhanced at, for example, 30 minutes. This onset of lysing activity is important in acute care situations.

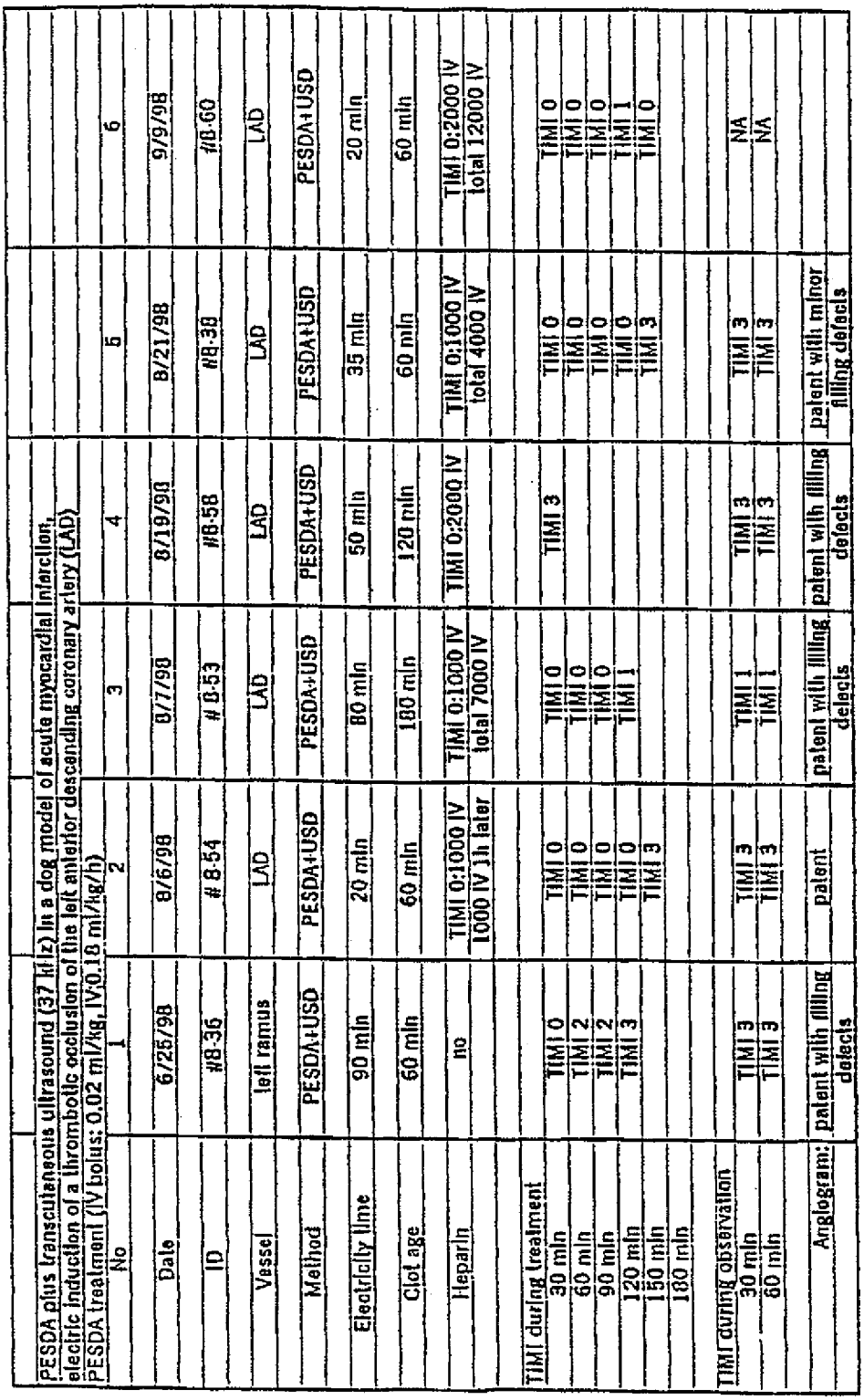
Further, the results utilizing ultrasound and tPA and PESDA, a sonicated albumin perfluorocarbon are shown in Tables 1 and 2. The data shown in Tables 1 and 2 on lysing of clots formed by electric induction of thrombotic occlusion of the left anterior descending coronary artery (LAD) to test the effects of PESDA and tPA in combination with transcutaneous ultrasound on reperfusion in a dog model in vivo. As indicated in the Tables, the ultrasound frequencies utilized were 26 kHz and 37 kHz. Heparin was also used in combination and the flow of blood through the arteries indicated as TIMI with a TIMI value of 0 representing no flow and a TIMI value of 3 representing unoccluded flow of blood. Other agents such as antiplatelet agents, such as GP IIb-IIIa inhibitor, microbubble mediums, anti-coagulants volume expanders and agents having a particulate nature such as Hetastarch, Pentaspan, as well as anticoagulants such as Heparin, produce similar results in vitro.

Tables 1 and 2 show data on ultrasound + PESDA and TPA + USD or TPA alone in a dog myocardial infarction model.

The results shown in Tables 1 and 2 indicate that PESDA which has no thrombolytic effect of its own facilitates ultrasound clot lysis in a coronary artery with there being re-establishment of blood flow in 5 of 6 dogs studied after the combination of intravenous PESDA and transcutaneous ultrasound over the dog's chest.

Table 2 shows that in comparison with intravenous tPA, (given in standard doses for humans) the standard thrombolytic drug given to patients with a heart attack, tPA only dissolves the clot in one of four dogs. Even in this case, there was residual clot in the coronary artery. However, when transcutaneous ultrasound over the dog's chest wall, aimed at the heart, is combined with the intravenous tPA, the clots are all dissolved, and there are no significant residual filling defects from blood clots. These data indicate that ultrasound plus a combination of a drug or drugs can be used to more effectively dissolve blood clots in the arteries of the heart to more effectively treat heart attacks.

Also incorporated into the present invention is a method, and corresponding apparatus 10, for treating a patient on a non-acute basis using the ultrasound methods hereinbefore displaced with agents which have no separate lysing activity but exhibit, or are activated, lysing activity when used in combination with ultrasound. As hereinabove noted, such agents include plasma volume expanders



PESDA plus transcutaneous ultrasound (37 kHz) in a dog model of acute myocardial infarction, electric induction of a thrombotic occlusion of the left anterior descending coronary artery (LAD)
PESDA treatment (IV bolus: 0.02 ml/kg, IV:0.18 ml/kg/h)

No	1	2	3	4	5	6
Date	6/25/98	8/6/98	8/7/98	8/19/98	8/21/98	9/9/98
ID	#8-36	# 8-54	# 8-53	#8-58	#8-38	#8-60
Vessel	left ramus	LAD	LAD	LAD	LAD	LAD
Method	PESDA+USD	PESDA+USD	PESDA+USD	PESDA+USD	PESDA+USD	PESDA+USD
Electricity time	90 min	20 min	80 min	50 min	35 min	20 min
Clot age	60 min	60 min	180 min	120 min	60 min	60 min
Heparin	no	TIMI 0:1000 IV 1000 IV 1h later	TIMI 0:1000 IV total 7000 IV	TIMI 0:2000 IV	TIMI 0:1000 IV total 4000 IV	TIMI 0:2000 IV total 12000 IV
TIMI during treatment						
30 min	TIMI 0	TIMI 0	TIMI 0	TIMI 3	TIMI 0	TIMI 0
60 min	TIMI 2	TIMI 0	TIMI 0		TIMI 0	TIMI 0
90 min	TIMI 2	TIMI 0	TIMI 0		TIMI 0	TIMI 0
120 min	TIMI 3	TIMI 0	TIMI 1		TIMI 0	TIMI 1
150 min		TIMI 3			TIMI 3	TIMI 0
180 min						
TIMI during observation						
30 min	TIMI 3	TIMI 3	TIMI 1	TIMI 3	TIMI 3	NA
60 min	TIMI 3	TIMI 3	TIMI 1	TIMI 3	TIMI 3	NA
Anglogram:	patent with filling defects	patent	patent with filling defects	patent with filling defects	patent with minor filling defects	

TABLE 1

Comparison of reperfusion using t-PA vs t-PA plus transcutaneous ultrasound (26 kHz) in a dog model of acute myocardial infarction, electric induction of a thrombotic occlusion of the left anterior descending coronary artery (LAD)

No	1	2	3	4	5	6	7
Date	12/24/98	12/31/98	1/15/99	1/19/99	1/21/99	1/28/99	2/12/99
ID	#B-84	#B-86	#B-87	#B-88	#B-89	#B-101	#B-97
Vessel	LAD	LAD	LAD	LAD	LAD	LAD	LAD
Method	t-PA alone	t-PA+USD	t-PA alone	t-PA+USD	t-PA+USD	t-PA alone	t-PA +USD
Electrically time	100 min	45 min	200 min	100 min	100 min	70 min	160 min
Clot age	60 min	90 min	120 min	120 min	120 min	120 min	360 min
Heparin	TIMI 0:2000 IV TIMI 3: 4000 SC	TIMI 0:1000 IV TIMI 3: 2000 SC	TIMI 0:1000 IV	TIMI 0:1000 IV TIMI 3: 2000 SC	TIMI 0:1000 IV TIMI 3: 1000 SC	TIMI 0:1000 IV TIMI 3: 1000 SC	TIMI 0:1000 IV TIMI 1: 1000 SC
TIMI during treatment							
20 min	TIMI 3	TIMI 3/15 min	TIMI 0	TIMI 1	TIMI 3	TIMI 3 with residual TI and distal occlusions	TIMI 0
40 min	N/A	N/A	TIMI 0	TIMI 1	TIMI 3	TIMI 0	TIMI 1
60 min	N/A	N/A	TIMI 0	TIMI 1	TIMI 3	TIMI 0	TIMI 1
90 min	N/A	N/A	TIMI 0	TIMI 1	TIMI 3	TIMI 0	TIMI 2
TIMI during observation							
30 min	TIMI 3	TIMI 3	N/A	TIMI 1	TIMI 3	TIMI 0	TIMI 3
60 min	TIMI 3	TIMI 3	N/A	TIMI 1	TIMI 3	TIMI 0	TIMI 3
90 min	TIMI 3	TIMI 3	N/A	TIMI 3	TIMI 3	TIMI 0	TIMI 3
90 min angiogram	patent with filling defects	widely patent	LAD occlusion	widely patent	widely patent	LAD occlusion	patent with minor filling defects
Serum analysis			Yes	Yes	Yes	Yes	Yes

TABLE 2

and colloid suspensions such as HESPAN® and PENTASPAN®.

Although there has been hereinabove described a specific arrangement of ultrasonic apparatus and method for thrombi dissolution in accordance with the present invention for the purpose of illustrating the manner in which the invention may be used to advantage, it should be appreciated that the invention is not limited thereto. Accordingly, any and all modifications, variations, or equivalent arrangements which may occur to those skilled in the art, should be considered to be within the scope of the present invention as defined in the appended claims.

WHAT IS CLAIMED IS:

1. Apparatus for effecting emergency treatment of a patient experiencing a thrombotic vascular occlusion, said apparatus comprising:

a plurality of active agents for dissolution of vascular occlusions, use of at least one of the active agents being selected on a basis of bleeding indication of the patient;

means for intravenously introducing a select agent into the patient; and

portable ultrasonic means of transcutaneously radiating the vascular occlusion.

2. The apparatus according to claim 1 wherein said plurality of active agents include at least one agent for use with a patient having no indicated bleeding, at least one agent for use with a patient having possible indicated bleeding and at least one agent for use with a patient having indicated bleeding.

3. A self-contained mobile unit for emergency treatment of a patient experiencing a thrombotic vascular occlusion, the unit comprising:

a plurality of active agents for dissolution of vascular occlusion, use of at least one of the active agents being selected on a basis of bleeding indication of the patient;

intravenous means for introducing a selected agent into the patient;

portable ultrasonic means for transcutaneously radiating the vascular occlusion; and

module means for storing the active agents, intravenous means and ultrasonic means.

4. The apparatus according to claim 3 wherein said plurality of active agents includes at least one agent for use with a patient having not indicated bleeding, at least one agent for use with a patient having possible indicated bleeding and at least one agent for use with a patient having indicated bleeding.

5. The apparatus according to claim 1 or 3 wherein at least one of the active agents is a microbubble medium.

6. The apparatus according to claim 5 wherein the micorbubble medium is comprised of a medium selected from the group comprising free gas bubbles, stabilized gas bubbles, colloidal suspension, emulsion and aqueous solutions.

7. The apparatus according to claim 1 or 3 wherein at least one of the active agents in a thrombotic agent.

8. The apparatus according to claim 1 or 3 wherein at least one of the active agents is an antiplatelet agent.

9. The apparatus according to claim 1 or 3 wherein at least one of the active agents is an anticoagulant.

10. The apparatus according to claim 1 or 3 wherein at least one of the active agent is a blood composition altering agent.

11. The apparatus according to claim 10 wherein said blood composition altering agents are selected

from a group consisting of a blood volume expansion agent, a blood replacement agent, a Hetastarch, Pentastarch and Dextran.

12. The apparatus according to claim 1 or 3 wherein at least one of the active agents in a intravenous fat emulsion.

13. The apparatus according to claim 12 wherein said intravenous fat emulsion is selected from a group comprising intralipid and liposyn.

14. The apparatus according to claim 1 or 3 wherein at least one of the active agents in a GP Iib-IIIa platelet inhibitor.

15. The apparatus according to claim 14 wherein the GP IIb-IIIa platelet inhibitor is Reopro.

16. The apparatus according to claim 1 or 3 wherein at least one of the active agents is a GP IIb-IIIa platelet blocker.

17. The method according to claim 16 wherein the GP IIb-IIIa platelet blocker is selected from a group comprising Aggrastat and Integrillin.

AMENDED CLAIMS

[received by the International Bureau on 26 June 2000 (26.06.00); original claims 1-17; replaced by new claims 1-15 (3 pages)]

1. Apparatus for effecting emergency treatment of a patient experiencing a thrombotic vascular occlusion, said apparatus comprising:

a plurality of active agents for dissolution of vascular occlusions, use of at least one of the active agents being selected on a basis of bleeding indication of the patient, said plurality of active agents including at least one agent for use with a patient having no indicated bleeding, at least one agent for use with a patient having possible indicated bleeding and at least one agent for use with a patient having indicated bleeding;

means for intravenously introducing the selected agent into the patient; and

portable ultrasonic means of transcutaneously radiating the vascular occlusion.

2. A self-contained mobile unit for emergency treatment of a patient experiencing a thrombotic vascular occlusion, the unit comprising:

a plurality of active agents for dissolution of vascular occlusion, use of at least one of the active agents being selected on a basis of bleeding indication of the patient said plurality of active agents including at least one agent for use with a patient having not indicated bleeding, at least one agent for use with a patient having possible indicated bleeding and at least one agent for use with a patient having indicated bleeding;

intravenous means for introducing a selected agent into the patient;

portable ultrasonic means for transcutaneously radiating the vascular occlusion; and

module means for storing the active agents, intravenous means and ultrasonic means.

3. The apparatus according to claim 1 or 2 wherein at least one of the active agents is a microbubble medium.

4. The apparatus according to claim 3 wherein the micorbubble medium is comprised of a medium selected from the group comprising free gas bubbles, stabilized gas bubbles, colloidal suspension, emulsion and aqueous solutions.

5. The apparatus according to claim 1 or 2 wherein at least one of the active agents in a thrombotic agent.

6. The apparatus according to claim 1 or 2 wherein at least one of the active agents is an antiplatelet agent.

7. The apparatus according to claim 1 or 2 wherein at least one of the active agents is an anticoagulant.

8. The apparatus according to claim 1 or 2 wherein at least one of the active agent is a blood composition altering agent.

9. The apparatus according to claim 18 wherein said blood composition altering agents are selected from a group consisting of a blood volume expansion agent, a blood replacement agent, a Hetastarch, Pentastarch and Dextran.

10. The apparatus according to claim 1 or 2 wherein at least one of the active agents in a intravenous fat emulsion.

11. The apparatus according to claim 10 wherein said intravenous fat emulsion is selected from a group comprising intralipid and liposyn.

12. The apparatus according to claim 1 or 2 wherein at least one of the active agents in a GP Iib-IIIa platelet inhibitor.

13. The apparatus according to claim 12 wherein the GP IIb-IIIa platelet inhibitor is Reopro.

14. The apparatus according to claim 1 or 2 wherein at least one of the active agents is a GP IIb-IIIa platelet blocker.

15. The method according to claim 14 wherein the GP IIb-IIIa platelet blocker is selected from a group comprising Aggrastat and Integrillin.

STATEMENT UNDER ARTICLE 19 (1)

INTERNATIONAL BUREAU OF WIPO
34, Chemin des Colombettes
1211 Geneva 20
SWITZERLAND

Gentlemen:

In response to an International Search Report, mailed 9 June 2000, the Applicant has limited the scope of the claims to the apparatus of the invention. No new matter is added by this amendment as the new claims correspond to originally filed claims as indicated in the letter accompanying the replacement pages. The present amendment replacing claims does not affect the original description or the original drawings.

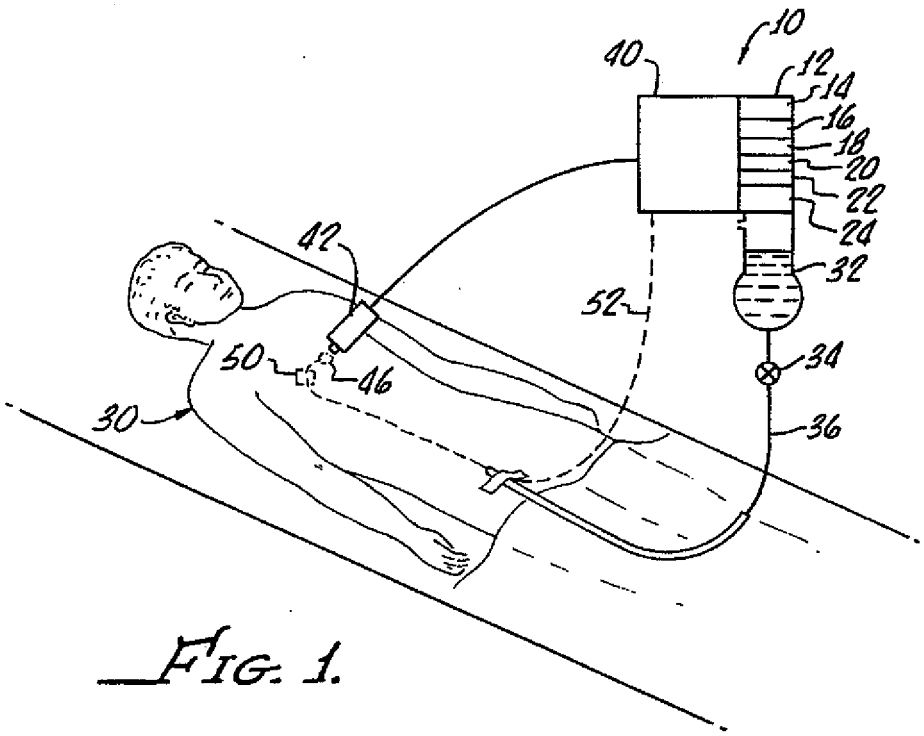

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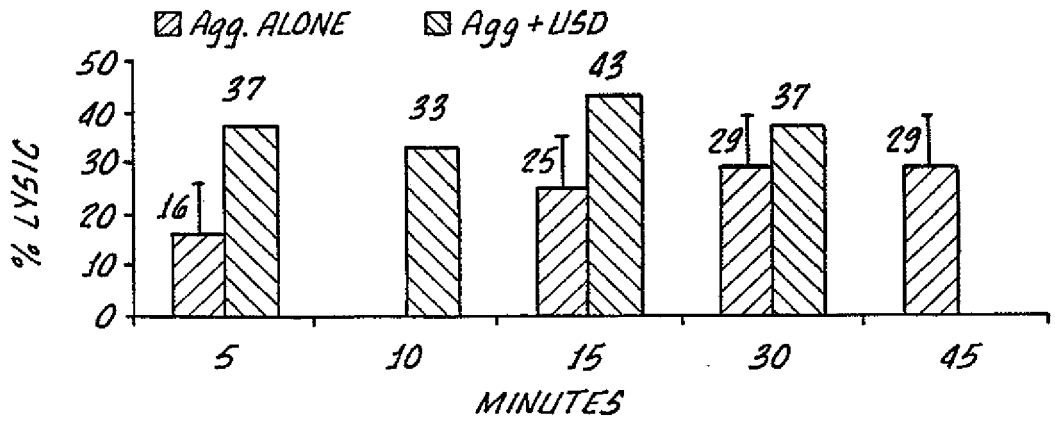
FIG. 1.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45
MINUTES

FIG. 2.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/07622

A. CLASSIFICATION OF SUBJECT MATTER
IPC(7) : A61M 31/00
US CL : 604/500
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 604/500

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EAST

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5,695,460 A [SIEGAL et al.] 19 December 1997, entire document.	1, 3, 5-7
X	US 5,380,273 A [DUBRUL et al.] 10 January 1995, entire document.	1, 3
Y	US 5,498,238 A [SHAPLAND et al.] 12 March 1996, entire document.	8-10
A,P	US 5,961,483 A [SAGE et al.] 05 October 1999, entire document.	14, 16
A,P	US 5,986,065 A [WONG et al.] 16 November 1999, entire document.	15
Y	US 5,498,421 A [GRINSTAFF et al.] 12 March 1996, entire document.	10-13

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 11 MAY 2000	Date of mailing of the international search report 09 JUN 2000
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer CATHERINE SERKE Telephone No. (703) 308-4846

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